PATENT

Attorney Docket No. 11823-002630US

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	
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QUEEN et al.	)	Examiner: Not Assigned
	)	
Serial No.: 08/484,537	)	Art Unit: 1806
	)	
Filed: June 7, 1995	)	INFORMATION DISCLOSURE
	)	STATEMENT UNDER
For: IMPROVED HUMANIZED IMMUNOGLOBULINS	)	37 CFR §1.97 and §1.98
	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants wish to bring the following information and the attached references, cited on the attached form PTO-1449, to the attention of the Examiner. Applicants submit the material for the voluntary consideration of the Examiner. If the Examiner will not consider the material, Applicants respectfully request that it be placed in the file wrapper of the subject application.

The filing of this IDS should not be construed as a representation that a search has been made or that no better art exists. No inference should be made that the information is in fact material or in fact prior art merely because of inclusion in this IDS.

In the following disclosure statement, international application WO 91/09967 of Adair et al. (the "Adair application"), which is believed to be the basis for pending U.S. patent application, is discussed, along with its priority application, GB 8928874, filed December 21, 1989. Reference is also made to a corresponding European patent, EP 0460167 (the "Adair EP patent"), currently in opposition proceedings based on the attached Opposition filed by Protein Design Labs, Inc. ("PDL").

For ease of reference, the specification of U.S. Patent No. 5,530,101 (the "'101 patent") will be used herein. The

present specification is a continuation of the '101 patent, and both have been assigned to PDL.

The '101 patent discloses several criteria developed by Queen et al. to produce humanized immunoglobulins. Specifically, selected amino acids from a donor immunoglobulin outside the Kabat and Chothia CDRs are substituted into an acceptor immunoglobulin framework in order to maintain high binding affinity (see columns 14 - 15) in the humanized immunoglobulin. These "Queen criteria" include: (i) that the donor amino acid be adjacent to a CDR in the immunoglobulin sequence ('101 patent column 14, lines 27 - 38), (ii) that the donor amino acid be capable of interacting with amino acids in the CDRs ('101 patent column 14, lines 39-51), e.g., because it contains an atom within 6 Å of them ('101 patent column 14, lines 55-58); or (iii) that the donor amino acid be typical at that position and the replaced acceptor amino acid be rare ('101 patent column 14, lines 1 - 17). In this regard, the Examiner is also referred to the '101 patent's priority patent application 07/290,975, filed December 28, 1988 (see, e.g., page 21, lines 23-34) (see also p. 31, line 12, through page 34, line 3 of the present application).

Similarly, the Adair application describes substitutions made in a mouse antibody designated OKT3 in order to produce a humanized OKT3 antibody with high binding affinity. The optimal humanized OKT3 variant contains four substitutions in the light chain at positions 1, 3, 46 and 47, and eleven in the heavy chain at positions 6, 23, 24, 48, 49, 71, 73, 76, 78, 88 and 91, outside the Kabat and Chothia CDRs (see light chain 221A and heavy chain 341A in Table 1 on p. 41 of the Adair application). *These precise positions form the basis and support of independent claims 1 and 6 of the Adair application.* <u>However, with the single exception of position 6 of the heavy chain, every one of these substitutions can be deduced from the Queen criteria listed above.</u> Indeed, PDL generated a model of the OKT3 antibody variable domain using methods described in the '101 patent (column 15, lines 43- 48). This model was used to determine which framework amino acids are capable of interacting with amino

acids in the CDRs, and are within 6 Å of the CDRs, as can be readily ascertained using computer graphics software described in the '101 patent (column 15, lines 53 - 57). Amino acids adjacent to the CDRs were determined by inspection of the sequence, while typical and rare amino acids were determined by reference to a sequence data bank. The attached Table shows that all 4 substituted positions in the humanized OKT3 light chain and 10 of the 11 such positions in the OKT3 heavy chain meet one of more of the Queen criteria.

To graphically highlight this point, attached are color photographs of a computer model of the OKT3 antibody variable domain. Figure 1A shows a front view of a wireframe model, with the light chain on the left and the heavy chain on the right, and Figure 1B shows a rear view of the same model, so the light chain is on the right. Figures 2A and 2B respectively show front and rear views of the same model in space-filling form. The Kabat and Chothia CDRs are shown in red. Those amino acids substituted in the Adair application that are capable of interacting with the CDRs, and thus meet Queen criterion (ii), are labeled and shown in blue (using the labeling convention that, e.g., CB (73H Lys) means the Lys amino acid at position 73 of the heavy chain). The pictures demonstrate that these amino acids are close to the CDRs, and measurement shows they are in fact within 6 Å of them. The amino acids 88H and 91H, where a typical donor amino acid replaces a rare acceptor amino acid, thus meeting Queen criterion (iii), are shown in yellow. The single amino acid, 6H, not apparently meeting the Queen criteria, is shown in magenta. Importantly, the amino acid substitution at 6 itself does not constitute anything of significance. The Adair application never shows that this particular substitution contributes to the affinity of humanized OKT3, only showing that the substitutions at 6, 23 and 24 *taken as a group* contribute. And it is much more likely that amino acids 23 and 24 (which are in fact capable of interacting with the CDRs) contribute to binding rather than the distant amino acid 6. Most importantly, the Adair application never shows that a substitution at position 6 contributes to the

affinity of *other* humanized antibodies. Hence, such a substitution appears to be merely a design choice, providing no teaching of any value to the skilled artisan.

In addition, it is respectfully submitted that the wording of the claims of the Adair application further indicate the lack of a cognizable contribution to the immunoglobulin humanization art. PDL is, of course, unaware of any specific pending claims in any U.S. patent applications corresponding to the Adair application, but the following discussion is at least relevant to understand any alleged contributions.

Thus, claim 1 of the Adair application is directed to a CDR-grafted antibody heavy chain wherein "the framework comprises donor residues" in at least one of certain specified positions (including 23 or 24), while claim 1 of the Adair EP patent similarly claims an antibody with a composite heavy chain in which certain amino acid residues (including 23 and 24) "are donor residues". Referring to the specifications of the Adair application and of the Adair priority document (GB 8928874) describing the making of the CDR-grafted (humanized) OKT3 antibody, the clear intent was that an actual *substitution* be made at the referenced positions, with a donor amino acid replacing a different acceptor amino acid. Indeed, actual substitutions at these positions were made in the optimal humanized OKT3 antibody and apparently were required to retain high binding affinity.

However, on the other hand, it appears that the Adair application claims attempt to encompass the situation when the donor and acceptor amino acids at the positions are *initially the same*, so that while technically the humanized framework comprises donor residues, no substitutions are actually required. For example, on p. 54 of the Adair patent application, it is asserted that a humanized OKT4A heavy chain is a preferred embodiment because "the murine and human residues are <u>identical</u> at all of positions 23, 49, 71, 73 and 78...." [emphasis added]. This is clearly a different, and apparently far broader concept, and creates other problems for the claims (as noted below). To make

sense, any claim in a U.S. patent application corresponding to the Adair application must be worded so as to make precise that actual substitutions (replacements) are required at specified positions.

On the contrary interpretation that amino acids which are initially the same in the acceptor and donor immunoglobulin at the specified positions meet the criteria of the claims, a humanized antibody with no actual substitutions at all, i.e., a straight CDR-grafted antibody, could be covered by the claims. Hence, the claims would lack novelty over U.S. Patent No. 5,225,539 of G. Winter (which was previously made of record in the present application's file wrapper).

Even under the interpretation that actual substitutions are required, claim 1 of the Adair application cannot issue in view of the '101 patent. For example, claim 1 would seem to attempt to encompass a CDR-grafted heavy chain having a donor residue in at least one of a list of positions, including 48. The humanized anti-Tac heavy chain disclosed in 1988 in the '101 patent's priority application has a donor substitution at position 48 (column 38, lines 8 - 10) of the '101 patent so again, claim 1 would lack novelty.

Finally, as also discussed on p. 35 - 38 of the enclosed PDL Opposition statement, several of the actual examples in the Adair EP patent show that the "rules" embodied in those claims do not in fact generally enable the production of humanized antibodies of sufficiently high affinity to be useful. The entire Opposition statement has been included for completeness.

If the Examiner believes that a telephone conference would clarify the above discussion or otherwise expedite the prosecution of the present application, please telephone the undersigned at (415) 326-2400.

Applicant believes that no fee is required for submission of this statement, since it is being submitted prior to the first Office Action. However, if a fee is required, the Commissioner is authorized to charge such fee to Deposit Account

No. 20-1430. Please charge any additional fees or credit any overpayment to the above-noted Deposit Account.

Respectfully submitted,

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Table. Amino acid substitutions Adair et al. patent application WO 91/09967 made according to criteria in specification of Queen et al., U.S. Patent No. 5,530,101.

Substitution in OKT3 by Adair et al. (WO 91/09967)	Meets "Queen" adjacent criterion (i)	Meets "Queen" interaction criterion (and within 6 Å) (ii)	Meets "Queen" rareness criterion (iii)
Light chain			
1	-	Yes	-
3	-	Yes	-
46	-	Yes	-
47	-	Yes	-
Heavy chain			
6	-	-	-
23	-	Yes	-
24	-	Yes	Yes
48	-	Yes	-
49	Yes	Yes	-
71	-	Yes	-
73	-	Yes	-
76	-	Yes	-
78	-	Yes	-
88	-	-	Yes
91	-	-	Yes